High Serum 25-hydroxyvitamin D is Associated with Low Incidence of Stress Fractures

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Original Article

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Abstract

Background: Low serum 25-hydroxyvitamin D [25(OH)D] concentrations are associated with hip fractures, but the dose-response relationship of serum 25(OH)D with risk of stress fractures in young women is unknown.

Objective: This nested case-control study in a cohort of female Navy recruits was designed to determine if those with low prediagnostic serum 25(OH)D concentrations had greater risk of stress fracture.

Design: Sera were drawn in 2002-2009 from 600 women who were subsequently diagnosed with stress fracture of the tibia or fibula, and 600 matched controls, who did not experience a stress fracture. The 25(OH)D concentration was measured using the DiaSorin radioimmunoassay method. Controls were individually matched to cases on race (White, Black, or other); length of service (± 30 days); and day blood was drawn (± 2 days).

Results: There was approximately half the risk of stress fracture in the top compared to bottom quintile of serum 25(OH)D concentration (OR = 0.51, 95% CI 0.34-0.76, $p \leq 0.01$). The range of serum 25(OH)D in the lowest quintile was 1.5-19.7 (Mean 13.9) ng/ml, while in the highest it was 39.9-112 (Mean 49.7) ng/ml.

Conclusions: There was a monotonic inverse dose-response gradient between serum 25(OH)D and risk of stress fracture. There was double the risk of stress fractures of the tibia and fibula in women with serum 25(OH)D concentration < 20 ng/ml, compared to those with ≥ 40 ng/ml. A target for prevention of stress fractures would be a serum 25(OH)D concentration of ≥ 40 ng/ml, achievable with 4000 IU/day vitamin D_3 supplementation.

Key words: Serum 25-hydroxyvitamin D, vitamin D, stress fracture, bone, physical training

Introduction

Adequate vitamin D plays a central role in promoting calcium absorption and maintaining adequate serum calcium and phosphate concentrations, enabling normal bone mineralization and preventing hypocalcemia, and is essential for bone formation and resorption (1-4). Adequate serum concentration of 25-hydroxyvitamin D (25(OH)D) is associated with lower prevalence of osteomalacia (5-7) and lower incidence of stress fractures (8).

Serum 25[OH]D) is the most accurate indicator of vitamin D nutritional status, since it includes the effects of solar ultraviolet (UVB) exposure and oral intake from food and supplements, and it has a markedly longer half-life (approximately 3 weeks) than vitamin D (14 hours) or 1,25 $(OH)_2D$ (24 hours) (2, 4).

Skeletal stress fractures associated with cumulative trauma are common in military recruit populations, and are an important cause of early attrition from service (8-12). Such studies have revealed a higher incidence of stress fractures in females than males (13, 14). Another study found that, within race/ethnic groups, age-adjusted mean bone mineral density (BMD) was higher in men than women at all skeletal sites examined (pelvis, arms and lumbar spine) ($p < 0.05$) (15). Vitamin D deficiency is associated with incidence of fractures in older adults of both sexes (16), a relationship between vitamin D deficiency and risk of fractures in those 18-44 years old has only recently been identified (8, 9).

A randomized, placebo-controlled clinical trial by Lappe et al., reported that female recruits assigned to 800 IU/day of vitamin D_3 and 2000 mg/day of calcium had 20% lower incidence rate of stress fracture than the placebo group ($p \leq 0.01$) (9). Amenorrhea and age older than 25 years were also predictors of increased risk of stress fracture, while history of exercise was protective (9). In another study, serum 25(OH)D concentrations below the median (30 ng/ml) were associated with a higher odds ratio for stress fracture in young men (OR = 3.6; 95% Confidence Interval [CI] = 1.2, 11.1) (8).

This study provides the first dose-response relationship between serum concentrations of 25(OH)D and the risk of stress fracture, using sera collected before the fracture occurred.

Materials and Methods

This was a nested case-control study within a cohort of US Navy female recruits. Data and serum specimens for this study were collected for comprehensive military health surveillance and epidemiologic analysis in accordance with DoD Directive 6490.2, dated October 21, 2004, and DoD Instruction 6490.3, dated August 7, 1997. The data are stored in the Defense Medical Surveillance System (DMSS), the central repository of medical surveillance data for the US armed forces, that contains up-to-date and historical data on disease incidence and other medical events, and longitudinal data on personnel and deployments. The DoDSR has been used for previous epidemiological research (17).

Sera from all active-duty service members, including recruits at the time of service entry, were collected by the DoD for surveillance and research purposes (18). The study population for this nested case-control study consisted of 1,200 Navy female recruits, including 600 cases and 600 controls. Incident cases of stress fracture of the tibia or fibula that met the case definition and had stored sera were included in the study. The case definition was: A stress fracture of the tibia or fibula (ICD 9-CM codes 733.16 or 733.93) identified in the first or second diagnosis positions, which occurred during the first 180 days of active-duty service between January 1, 2002, and June 30, 2008, in female recruits. The most recent serum samples preceding the date of stress fracture were obtained.

Each case was individually matched to a female control by the following criteria: Age (± 2 years); race/ethnicity (non-Hispanic White, non-Hispanic Black, or other); length of service equal to that of the case ± 30 days; and blood drawn within ± 2 days of the case. All controls were on active duty within ± 30 days of the date of diagnosis of stress fracture in the case. Hispanic persons were considered white. If more than one potential control met the criteria, the control whose date of serum collection was closest to that of the case was selected.

Independent variables included serum 25(OH)D concentration, body mass index (BMI) and state of residence at entry into the military. BMI was included since heavier individuals have higher hip BMD and more robust femur geometry (19). Furthermore, BMI and body weight are inversely associated with 25(OH)D concentrations (20, 21). PTH concentration was not available.

BMI was calculated by dividing body weight in kilograms by body height in meters squared. Weight and height measurements were available on 594 case-control pairs. Home of residence was included since 25(OH)D concentrations are usually inversely related to latitude (22). Quarter of first diagnosis of stress or pathological fracture while in the military was categorized as: Winter (Jan-Mar), Spring (Apr-Jun), Summer (Jul-Sep), and Autumn (Oct-Dec). Latitude of residence was determined by state or territory of residence at entry into the military. Northern latitudes were arbitrarily defined as states or territories 41^{o} latitude or higher; middle latitudes were states or territories between 37^{o} and 40^{o} latitude; and southern latitudes consisted of states or territories lower than 37^{o} latitude.

No data were available on history of oral intake of vitamin D before joining the military.

Univariate and multivariate analyses were performed using the SAS version 9.1 conditional logistic regression procedure (PROC LOGISTIC) (Cary NC: SAS Institute). Quintiles of serum 25(OH)D were defined based on the control population. Odds ratios of stress fracture were determined using the lowest quintile of serum 25(OH)D in the control population as the reference category. The criterion for statistical significance was $p \leq 0.05$, two-tailed.

This study used aliquots of 0.5 ml each of frozen serum samples stored in the DoDSR to determine pre-fracture circulating serum 25(OH)D concentrations for cases and their matched controls. Samples were analyzed blindly at Heartland Assays Inc. in Ames, IA, using acetonitrile and a radioimmunoassay method (23).

This study was conducted in accordance with the ethical standards of the relevant Department of Defense Institutional Review Board (IRB) and the Helsinki declaration of 1975, as revised in 1983, and IRB approval was obtained.

Results

The majority of recruits with stress fracture were white (54.4%) and aged 20 years or younger (80.0%; mean age, 19.5 years) (Table 1). The mean serum 25(OH)D concentration was 28 ng/ml in cases and 31 ng/ml in controls. In the overall population, the mean and median serum 25(OH)D concentration were 30 ng/ml. Blacks had the lowest mean 25(OH)D concentrations in both cases and controls (16 ng/ml in cases compared to 20 ng/ml in controls) (Table 1). The mean BMI was 23.9 in cases and 24.2 in controls (Table 1).

Women in the highest quintile of serum 25(OH)D (range 39.9-112.5 ng/ml; mean 50 ng/ml ± standard deviation [SD] 10 ng/ml) had lower risk of stress fractures than those in the lowest quintile (range 1.5-19.7 ng/ml; mean 14 ng/ml ± SD 4 ng/ml; odds ratio [OR] = 0.51; 95% CI = 0.34, 0.76; $p \leq 0.01$) (Figure 1). There was a dose-response relationship of higher serum 25(OH)D concentration with lower risk of stress fracture ($p_{trend} = 0.02$) (Figure 1). There was no association between BMI or latitude of home of residence and risk of stress fracture. Latitude of home of residence was included in the multivariate regression model since it was associated with risk at the $\alpha = 0.10$ level of significance ($p = 0.06$). The association was tested using linear and nonlinear models.

The association of serum 25(OH)D concentration with risk of stress fractures also was analyzed by race. Quartiles were used for whites and other races, while division at the median was used for blacks, who were the demographic group with the fewest (n = 71) cases.

There was a clear inverse dose-response gradient in white women, similar to that for women of all races combined. In white women, ranges and means for quartiles of serum 25(OH)D ng/ml and corresponding odds ratios were as follows:

Quartile 1, range = 6.5 – 26.9 ng/ml, mean = 20 ng/ml, OR = 1.0, (reference group); Quartile 2, range = 27 – 33.4 ng/ml, mean = 30 ng/ml, OR = 0.68, 95% CI = 0.44, 1.1; Quartile 3, range = 33.5 – 40.1 ng/ml, mean = 37 ng/ml, OR = 0.57, 95% CI = 0.36, 0.89; Quartile 4, range = 40.2 – 112.5 ng/ml, mean = 50 ng/ml, OR = 0.49, 95% CI 0.31, 0.79; (p trend = 0.02).

Serum 25(OH)D concentrations among white women in the highest quartile (40.2-112.5, mean 50 ng/ml) were associated with half the risk of stress fracture as those in the lowest quartile (6.5-26.9, mean 20 ng/ml) ($p \leq 0.05$). Blacks with serum 25(OH)D concentrations above the median (20 ng/ml) had a substantial, although statistically borderline, lower risk of stress fracture than blacks below the median (OR = 0.54; 95% CI = 0.28, 1.06; $p = 0.07$). In women of other races, no association was observed in this study between serum 25(OH)D concentration and risk of stress fracture.

In the multivariate regression model, serum 25(OH)D concentration persisted as being inversely associated with risk of stress fracture ($p_{trend} = 0.02$) (Table 2). The association of latitude of home with odds ratios for stress fractures remained borderline ($p = 0.07$). Similar to the univariate analysis, risk of stress fractures was lowest in individuals whose serum 25(OH)D concentration was in the highest quintile (39.9-112.5 ng/ml) compared to those in the lowest quintile (1.5-19.7 ng/ml) (OR, 0.51; 95% CI = 0.34, 0.78; $p = 0.01$). For latitude of home of residence, persons living in southern latitudes at the time of entry into the Navy had a higher risk of stress fracture (OR, 1.43; 95% CI = 1.05, 1.95; $p = 0.05$).

Discussion

An inverse association between serum 25(OH)D and risk of stress fracture was not detected among blacks or individuals of other races, although the finding in blacks approached statistical significance. Previous data suggest that blacks have higher mean total bone mineral density than whites (15). Our inability to detect an association of serum 25(OH)D with risk of stress fracture may be due to overall higher bone mineral density in blacks (15). The positive association with serum 25(OH)D, although of borderline statistical significance, suggests that vitamin D still could be of value for prevention of stress fractures in blacks. A larger observational study or randomized controlled trial similar to that of Lappe et al. (9), could help in further evaluation of this association.

Another possible explanation for the lack of a statistically significant association between serum 25(OH)D level and lower risk of fractures in blacks is the low concentration of serum 25(OH)D found in this population. Due to increased levels of skin pigmentation, blacks synthesize 25(OH)D at one-third the rate as Caucasians (24). In this study, blacks had mean serum 25(OH)D concentrations that were approximately half those of whites (Table 1). Since the greatest statistically significant reduction in risk was found in subjects in the highest quintile of serum 25(OH)D (39.9-112.5 ng/ml), serum 25(OH)D in black subjects may not have been high enough for a protective effect on fractures to occur.

Previous research has shown that amenorrhea and history of exercise were independently associated with risk of fractures (9). In this study, it was not possible to include amenorrhea and exercise history (prior to basic training) in the regression model as confounders because data on these factors were not available for the population under study. Therefore, results of the analysis should be interpreted with caution. However, all recruits undergo the same training regimen in basic training. Therefore, all recruits have the same exercise history with respect to basic training.

No association was detected between latitude of home of residence and risk of stress fracture. This was unexpected, since there are greater amounts of solar ultraviolet B exposure at lower latitudes. Home of residence is the location of residence indicated at the time of entry into the military. The home of residence variable does not take into account the length of time spent in a particular state or territory, and is not necessarily indicative of usual location or the location of birth. Alternatively, persons living in southern latitudes may use sunscreen more frequently, preventing solar ultraviolet B from penetrating the skin to synthesize vitamin D.

BMI over the range observed in the study population was not associated with risk of stress fracture. BMI was analyzed as a continuous rather than categorical variable because the standard categories associated with BMI ranges are specific to adults 20 years old and older, and the majority (61%) of our study population was aged 19 years or younger.

Data on other sites of lower extremity stress fracture were not available. Stress fractures of the pelvis, femoral neck and shaft, other parts of the femur, metatarsals, and other lower extremity sites were formerly classified under general ICD-9-CM codes and the site of stress fracture had to be specified separately. Because the specific site affected was not available in the database, only fractures of the tibia and fibula could be identified. However, in military recruits the most common sites of stress fractures are the tibia and fibula (9).

The present study may be interpreted in the context of the findings of a study by Priemel et al. (6), who examined iliac crest bone biopsies in Germany, and found that pathological accumulation of osteoid was only completely prevented when the circulating 25(OH)D concentration was > 30 mg/ml. The authors concluded that 30 ng/ml of 25(OH)D is the minimum circulating concentration to maintain bone health. The present study confirmed this assertion, but our data suggest that 40 ng/ml would be a more appropriate target for 25(OH)D with regard to prevention of stress fractures, since the risk of stress fractures continued to be lower through at least 40 ng/ml.

Both the proposed 30 and 40 ng/ml targets for bone health are higher than the 20 ng/ml target for 25(OH)D concentration proposed by the Committee to Review Dietary Reference intakes for Vitamin D and Calcium, of the National Academy of Sciences-Institute of Medicine, Food and Nutrition Board (25). It is possible that the committee may have included only the data points for observed excessive osteoid volume above 2% solely from the subjects whose serum 25(OH)D concentration also was < 20 ng/ml. Such an analysis would have excluded at least 6 data points where osteoid volume was excessive and the subjects' serum 25(OH)D concentration was higher than 20 ng/ml. It is not clear why or whether these data points were excluded. If they had they been included, they would have indicated that 30 ng/ml, rather than 20 ng/ml, was the minimal 25(OH)D concentration threshold for preventing excessive osteoid volume, and the minimum target for maintaining bone health. Based on the present study, it appears that a higher serum 25(OH)D concentration, specifically 40 ng/ml, would be a more appropriate target for maintaining bone health with respect to stress fractures of the tibia and fibula.

There was either a lack of a statistically significant benefit – or, alternatively, a beneficial trend of borderline significance – between serum 25(OH)D concentration and risk of stress fracture in African-Americans in the present study. This finding is reminiscent of the lack of association between prediagnostic serum 25(OH)D concentration and risk of multiple sclerosis in African-Americans in an earlier study (17).

In that study, African-Americans had lower risk of multiple sclerosis than whites, and there was no significant association of serum 25(OH)D concentration with risk of the disease (17). To account for this racial difference, the authors proposed that a gene associated with racial admixture (26) might have reduced the incidence of multiple sclerosis, and its association with low 25(OH)D concentration, in African-Americans. On the other hand, though, the dose-response gradients for the association of lower serum 25(OH)D concentration with higher risk of stress fracture were similar in African-Americans and whites in the present study. All considered, low serum 25(OH)D concentration appears be associated with risk of stress fractures of the tibia and fibia, probably regardless of race. However, more research would help to confirm this, since the findings in African-Americans were borderline."

The latitude of training is that of Great Lakes IL, 43 degrees N. The military does not, at present, routinely provide 25(OH)D testing or vitamin D supplements to recruits.

Risk of stress fractures was paradoxically higher in recruits who identified the South as their home of record. It is possible that regional differences in per capita dietary intake of calcium could at least partly account for the higher rate of stress fractures in women from the South, since lower intake of calcium in the South might theoretically contribute to higher risk of osteomalacia, potentially a precursor of fractures. Per capita mean intake of dietary calcium is somewhat lower in the South (685 mg/d) than in the North Central (755 mg/d) or Northeast (728 mg/d) sectors of the US (27). Race may also have contributed this finding, since the incidence of stress fractures was substantially lower in black than white women, and recruits from the South were more likely than those from other regions to be black.

The findings in this study emphasize the importance of vitamin D status in risk of stress fractures in young women who are taking part in physical activity. Although this study was conducted in a military population exposed to rigorous physical training over an eight-week period, vitamin D is also likely to benefit young women in the general population who engage in strenuous physical activity. This could include females who take part in high school or college athletic programs, marathons and/or triathlons, and moderate to high impact weight-bearing activities. Women with a history of stress fracture may also benefit from the findings of this study. Recent studies have shown that vitamin D deficiency is highly prevalent in otherwise healthy young people (28-30).

Since the risk of fractures increases in older adults, and fractures can occur at any age, vitamin D supplementation is recommended for all ages. According to the Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine (IOM) - National Academy of Sciences - the current recommended daily intake of Vitamin D for persons from birth to 50 years is 200 IU vitamin D per day, 51 to 70 years is 400 IU per day, and 71 years and older is 600 IU per day (2). Historically, serum 25(OH)D concentrations ≥ 20 ng/ml (or ≥ 50 nmol/L) have been considered adequate for bone and overall health in healthy individuals (2). However, based on the findings of this study, only serum 25(OH)D concentrations in the highest quintile (39.9-112.5 ng/ml) were associated with lower risk of stress fractures. A similar association was present when the comparison was limited to whites (40.2 to 112.5 ng/ml).

The lowest serum 25(OH)D concentration shown to adequately reduce the risk of stress fracture was at least double the formerly recommended minimum serum concentration (>20 ng/ml) (2). In normal adults, 4,000 IU per day of vitamin D_3 would be needed to maintain serum 25(OH)D concentrations no less than 100 nmol/L or 40 ng/ml (31). Although 25(OH)D concentrations up to 400 ng/ml (or 1,000 nmol/L) were not detected as being associated with harm in an animal model (32), no randomized controlled trials have been conducted to establish the safety of 2,000-4,000 IU/day by young adults.
While no randomized trials of vitamin D3 intakes of 2000–4000 IU/day have been reported, the 2010 IOM Report endorsed 4000 IU/day as being the Tolerable Upper Level of Intake (TULI)(2).

According to the present study, 75% of female recruits were at higher than necessary risk of stress fractures of the tibia and fibula due to low serum 25(OH)D concentrations (< 40 ng/ml). The higher risk of stress fractures due to low serum 25(OH)D could be addressed in young women by assuring their serum 25(OH)D concentration is maintained at 40 ng/ml or higher.

The present study did not measure serum 25(OH)D concentrations in male recruits. Therefore, it is not known from this study whether a similar association of lower serum 25(OH)D concentrations with higher risk of stress fractures applies to males. However, a previous study by Ruohola et al. in Finland, identified such an association in males that is similar to that of the present study of females (8). It is reasonable to expect that the association found in the present study in women would also be present in men, considering the findings of Ruohola et al. (8). Future research on male recruits would be desirable to confirm this, though, in the US or other countries.

Vitamin D intake has been reported to be safe for adults in doses up to 9,000 IU/day (33). Full-body solar exposure provides the equivalent of 10,000 IU/day, suggesting that this may be a physiologic limit (31, 34, 35). These results suggest that supplementary vitamin D_3 intakes of 2,000 - 4,000 IU/day would promote bone health and reduce risk of stress fractures, and that the benefits of this intake would exceed its risks.

Recruit training begins shortly after entry into the US military. It may be beneficial to test serum 25(OH)D concentrations at military processing centers to identify individuals at higher risk of fracture during recruit training. Vitamin D supplementation during boot camp has been shown to decrease the risk of stress fracture in female Navy recruits (9). Vitamin D_3 supplementation prior to boot camp would be even more beneficial, since it may take 2-3 months to increase serum 25(OH)D concentrations to optimal in those who are insufficient.

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Duties of the authors:

Ms. Burgi performed the statistical analyses, arranged for access to the DoD blood samples, wrote the first and several subsequent drafts of the manuscript, and incorporated reviews by coauthors in the period preceding submission; Dr. Gorham coordinated the overall concept and design of the study, proposed statistical analyses, and reviewed and approved multiple drafts of the manuscript; Dr. Cedric Garland helped with the overall concept and design of the study and reviewed and approved multiple drafts of the manuscript; Mr. Mohr reviewed and approved drafts of the manuscript and made numerous key edits to the manuscript; Dr. Frank Garland proposed the concept and design of the study, and reviewed and approved multiple drafts of the manuscript; Mr. Zeng reviewed the literature on vitamin D and stress fractures, reviewed the manuscript, provided literature citations, and shared in the drafting of revisions; Drs. Thompson and Lappe offered important suggestions regarding design of the study, proposed the diagnostic inclusion criteria, and reviewed and approved drafts of the manuscript.

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Figure Legend

Figure 1. Odds ratios and 95% confidence limits for incident stress fracture of the tibia or fibula (ICD-9 codes 733.16, 733.93) occurring within 180 days of enlistment, by prediagnostic serum 25-hydroxyvitamin D level among 600 cases and 600 matched controls, female Navy recruits, 2002-2008. Cases were matched to controls by age, date of blood draw, race and service entry date.

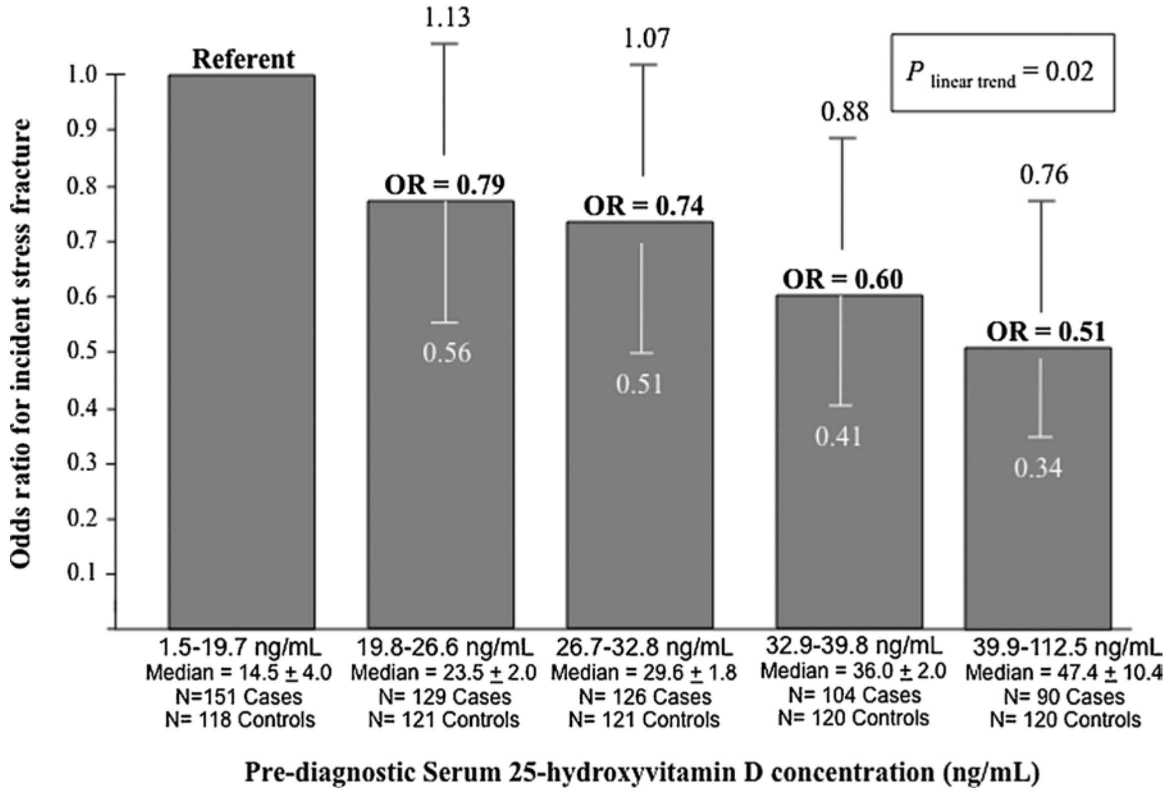
Table 1. Characteristics of cases and controls, US Navy female recruits, 2002-2008.

Variable	Cases (n=600)	Controls (n=600)
Race (%)		
White	326 (54.4)	326 (54.4)
Black	71 (11.8)	71 (11.8)
Other races	203 (33.8)	203 (33.8)
Mean age in years (± standard deviation)	19.5 (±1.8)	19.5 (±1.6)
Serum collected (%)		
Winter (Jan-Mar)	93 (15.5)	93 (15.5)
Spring (Apr-Jun)	159 (26.5)	159 (26.5)
Summer (Jul-Sep)	256 (42.7)	256 (42.7)
Autumn (Oct-Dec)	92 (15.3)	92 (15.3)
Mean BMI (± standard deviation)	23.9 (±3.0)	24.2 (±10.1)
Mean serum 25(OH)D, ng/ml (± standard deviation)*	28.2 (±12.1)	30.9 (±13.5)
Whites	31.5 (±11.2)*	34.8 (±13.2)*
Blacks	16.0 (±7.4)*	19.6 (±10.0)*
Other races	27.2 (±11.9)	28.6 (±12.4)

* $p < 0.05$ according to unpaired t-test

Table 2. Multivariate analysis of stress fracture and serum 25(OH)D concentration and home of residence using conditional logistic regression in 600 cases and 600 controls, 2002-2008

Variable	Regression coefficient	Standard error	Odds ratio	95% Confidence interval	*P* value for stratum	Overall *P* value
Serum 25(OH)D range (mean) ng/ml						0.02
1.5-19.7 (13.9)	---	---	1.00	---	---	---
19.8-26.6 (23.2)	0.082	0.117	0.77	0.54, 1.11	0.48	---
26.7-32.8 (29.8)	0.058	0.119	0.76	0.52, 1.10	0.63	---
32.9-39.8 (36.4)	-0.149	0.121	0.61	0.42, 0.91	0.04	---
39.9-112.5 (49.7)	-0.329	0.130	0.51	0.34, 0.78	0.01	---
Home of residence (latitude)						0.07
Northern	---	---	1.00	---	---	---
Middle	0.040	0.092	1.27	0.91, 1.78	0.66	---
Southern	0.159	0.082	1.43	1.05, 1.95	0.05	---



Odds ratio for incident stress fracture
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Referent
1.13
OR = 0.79
0.56
1.07
OR = 0.74
0.51
0.88
OR = 0.60
0.41
0.76
OR = 0.51
0.34
P linear trend = 0.02
1.5-19.7 ng/mL
Median = 14.5 ± 4.0
N=151 Cases
N= 118 Controls
19.8-26.6 ng/mL
Median = 23.5 ± 2.0
N= 129 Cases
N= 121 Controls
26.7-32.8 ng/mL
Median = 29.6 ± 1.8
N= 126 Cases
N= 121 Controls
32.9-39.8 ng/mL
Median = 36.0 ± 2.0
N= 104 Cases
N= 120 Controls
39.9-112.5 ng/mL
Median = 47.4 ± 10.4
N= 90 Cases
N= 120 Controls
Pre-diagnostic Serum 25-hydroxyvitamin D concentration (ng/mL)

Figure 1

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13. SUPPLEMENTARY NOTES

14. ABSTRACT (maximum 200 words)

Low serum 25-hydroxyvitamin D [25(OH)D] levels cause rickets and osteomalacia, but it is unknown whether the condition increases risk of stress fractures in young adult. This study was conducted to determine if young women with low serum 25(OH)D have an increased risk of stress fracture compared to those at higher levels.

Methods. The Department of Defense has collected and frozen serum from over nine million service members. Pre-fracture serum specimens from 600 female cases of stress fracture of the tibia or fibula that occurred during the first 180 days of active-duty were analyzed for 25(OH)D content. Specimens from 600 controls, individually matched to the cases on age (+/-2 years);race (white, black or other); length of service +/- 30 days; who had blood drawn within 2 days of the case; and were on active duty within 30 days of the case's diagnosis also were analyzed.

Findings: Higher serum 25(OH)D levels were associated with lower risk of stress fracture (*p* =0..02). A linear dose-response relationship with increasing serum 25(OH)D revealed 50% lower risk of stress fracture in the top compared to the bottom quintile (*p* trend = 0.02). Women in the lowest quintile (≤ 19.7 ng/ml) had a mean 25(OH)D of 13.9 ng/ml (standard deviation [SD] +/-4.0), while those in the highest ≥ 39.9 had a mean of 49.7 ng/ml (SD +/- 10.4 ng/ml).

Interpretation. Lower incidence of stress fracture in women with serum 25(OH)D greater than approximately 40 ng/ml indicates a minimum clinical target for prevention.

14. SUBJECT TERMS
Vitamin D, stress fracture, tibia, fibula, serum 25 (OH) vitamin D, epidemiology, military Navy

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